REMARKS

Upon entry of this Amendment, claims 1-19, 23-25 and 30 will be pending. Claims 20-22 and 26-29 have been withdrawn without prejudice or disclaimer. Claims 1, 3, 4, 5, 6, 7, 10, 11, 14, 23 and 30 have been amended to more clearly define the present invention. Applicant asserts that no new matter has been added by way of these amendments.

Claims 1 and 5 have been amended to define the length of the antisense oligonucleotide as being from about 15 to about 100 nucleotides. Support for this amendment can be found on throughout the specification as filed. Support for the amendments to the claims to recite "a human neuropilin mRNA" can be found at page 11, lines 15 to 22 and page 20, lines 12 to 14.

Election/Restriction

In response to the final restriction requirement issued by the Examiner, Applicant has limited the claims to Group I, claims 1-30, including SEQ ID NO:33.

Rejection of Claims under 35 U.S.C § 112, First Paragraph (Written Description)

The Examiner has rejected claims 1–25 and 27–30 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the claims are adequately described for design of antisense to SEQ ID NO:33 only. Applicant respectfully disagrees, but in order to expedite prosecution of the instant application, Applicant has amended the claims to recite antisense oligonucleotides complementary to SEQ ID NO:33. Accordingly, Applicant respectfully requests withdrawal of this rejection.

The Examiner has further alleged that claims 5-22 and 27-30 are not considered adequately described by the specification "since the specification as filed does not provide via specific sequence structure a representative number of species of antisense oligonucleotides to human neuropilin gene, elected SEQ ID NO:33, having a specific correlation or nexus to the claimed treatment functions in a whole organism."

Applicant respectfully traverses. MPEP 2163 states that in order to satisfy the written description requirement, a patent specification must "describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Possession can be shown by describing the claimed invention "using such

descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." Applicant asserts that the specification as filed provides detailed teaching regarding selection and preparation of appropriate antisense oligonucleotides for use in the claimed methods and compositions (see, for example, at page 15, lines 1 to 15 and page 22, line 12 to page 25, line 10), as well as pharmaceutical formulations comprising the antisense oligonucleotides (see, for example, at page 25, line 11 to page 34, line 14) and methods of using the antisense oligonucleotides in the treatment of cancer (see, for example, at page 34, line 15 to page 36, line 7). Furthermore, the instant specification provides detailed teaching of methods to screen these antisense oligonucleotides for their ability to inhibit neuropilin expression *in vitro* (see Example 2) and to inhibit tumor growth and metastasis *in vivo* (see Examples 3 and 4).

Moreover, as amended, claims 5 – 19 define the antisense oligonucleotides, not only in terms of function (*i.e.* that the antisense oligonucleotide specifically binds to a nucleic acid comprising a sequence corresponding to a human mRNA and inhibits neuropilin expression), but also in terms of structure (*i.e.* comprising at least 15 consecutive nucleotides from a sequence complementary to a human neuropilin mRNA [SEQ ID NO:33]). As indicated by the Examiner, MPEP 2163 states that the written description requirement for a claimed genus may be satisfied by "actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics" for a representative number of species.

Applicant has demonstrated the activity for a representative number of the claimed antisense oligonucleotides in inhibiting the growth of cancer cells *in vitro* (see Example 1) and has gone on to show that this *in vitro* activity correlates to inhibition of the growth and/or metastasis of cancer cells *in vivo* (see Examples 3 and 4). Applicant submits, therefore, that a worker skilled in the relevant art having regard to the instant specification would conclude that the Applicant was in possession of the claimed genus at the time the application was filed. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of Claims under 35 U.S.C § 112, First Paragraph (Enablement)

The Examiner has rejected claims 5-22 and 27-30 under 35 U.S.C. 112, first paragraph, stating that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner alleges that the specification "does not reasonably provide enablement for "pharmaceutical compositions" of antisense neuropilin, nor methods of administering the claimed antisense *in vivo* for the claimed treatment effects." The Examiner has further cited several new references and has alleged that these references "provide teachings of the high level of unpredictability in the art for the use of any antisense oligonucleotide *in vivo*, and the lack of correlation in the art between mice and humans for cancer."

Again, Applicant respectfully traverses. As indicated in MPEP 2164, "The test for enablement is whether one reasonably skilled in the art could make or use the invention from the

disclosures in the patent coupled with information known in the art without undue experimentation." Applicant maintains, for the reasons set forth in the Responses filed on March 28, 2001 and April 19, 2002, that a worker skilled in the relevant art would be able to practice the invention as claimed without undue experimentation. Contrary to the assertion by Jen *et al*, that "effective and efficient clinical translation of the antisense strategy has proven elusive," Applicant notes that several antisense reagents have in fact reached clinical trials for a variety of indications including leukemia, cancer and AIDS, as is readily apparent from the clinical trials listing provided by the National Institute of Health. For example, ISIS 2302 is currently in Phase III clinical trials for Crohn's disease and G3139 (Oblimersen) is currently is in Phase III clinical trials for various cancers. ISIS 3521 and a number of other ISIS antisense oligonucleotides are currently in Phase II clinical trials. As noted previously, Vitravene™ received regulatory approval in 1998. Furthermore, Ma *et al.*, Jen *et al.* and Green *et al.* all describe some level of clinical efficacy in antisense clinical trials.

Moreover, Applicant respectfully disagrees with the Examiner's assertion that the new references provide teachings of a "lack of correlation between mice and humans for cancer." As discussed in Applicant's Response dated March 28, 2001, human tumor xenograft models were recognized in the art at the time of filing the instant application as good predictive tools for clinical effectiveness of anti-cancer treatments. Many of the problems associated with the mouse models discussed in both Sigmund and Blackshear relate specifically to transgenic mice and, therefore, are not generally applicable to human tumor xenograft models. Transgenic mice are

used to study the role and/or effects of certain genes that are either endogenous or which have been introduced into the mouse genome. In contrast, xenograft models study the effects of drugs on human cancer cells implanted into a mouse. Many of the antisense oligonucleotides discussed above that are currently in clinical trials were initially tested *in vitro* or in mouse models. For example, the antisense molecules G3139 and ISIS 3521 were originally selected on the basis of results obtained in murine models.

In conclusion, Applicant submits that antisense therapy is no more "unpredictable" than other therapies and requires only the customary testing and/or screening that is associated with the development of any new pharmaceutical. In order to be enabling, the specification must simply demonstrate that the invention works as claimed and provide sufficient guidance to allow one skilled in the art to make and use the invention as claimed. Applicant maintains that the instant specification meets with these requirements and, therefore, respectfully requests reconsideration and withdrawal of the present rejection.

Rejection of Claims under 35 U.S.C. § 102

The Examiner has rejected claims 1, 3 and 5 under 35 U.S.C. 102(b) as being anticipated by EST database AA048244. EST database AA048244 discloses an oligonucleotide of 37 bases corresponding to bases 1827-1863 of instant SEQ ID NO:33, with a one base mismatch. SEQ ID NO:33 of the instant application corresponds to the mRNA sequence from a human neuropilin gene as described in the specification at, for example, page 20, lines 12 to 14. The antisense

oligonucleotides of the instant invention as described, for example, at page 11, lines 15 to 22, are complementary to a mammalian neuropilin mRNA (including SEQ ID NO:33). Applicant has amended claims 1, 3 and 5 to more clearly define the claimed antisense oligonucleotides, specifically to replace the phrase "a transcribed region of a human or rodent neuropilin gene" with the phrase "a human neuropilin mRNA, wherein said mRNA has a sequence as set forth in SEQ ID NO:33." Support for this amendment can be found for example, at page 11, lines 15 to 22 and page 20, lines 12-14. Thus, contrary to the Examiner's assertion, the antisense oligonucleotides have a sequence that is complementary to, not the same as, the sequence set forth in SEQ ID NO:33. In contrast, the oligonucleotide disclosed in EST database AA048244 has a sequence that corresponds to a part of SEQ ID NO:33. Accordingly, Applicant submits that EST database AA048244 does not anticipate the subject matter of claims 1, 3 and 5 and respectfully requests reconsideration and withdrawal of this rejection.

The Examiner has rejected claims 1, 3, 5, 26 and 27 under 35 U.S.C. 102(b) as being anticipated by WO9507994/ N Geneseq database accession no. AAQ86161, which discloses an oligonucleotide of 21 bases corresponding to bases 2-16 of instant SEQ ID NO:5, with a one base mismatch. Applicant has withdrawn, without prejudice, claims 26 and 27 and has amended claims 1, 3 and 5. As amended, claims 1, 3 and 5 are drawn to antisense oligonucleotides from about 15 to about 100 nucleotides comprising at least 15 consecutive nucleotides from a sequence complementary to a human neuropilin mRNA (SEQ ID NO:33). The oligonucleotide disclosed in WO9507994/ N Geneseq database accession no. AAQ86161 comprises, at most, 14

consecutive nucleotides complementary to SEQ ID NO:33. Applicant submits that WO9507994/ N Geneseq database accession no. AAQ86161 does not anticipate the subject matter of amended claims 1, 3 and 5 and, therefore, respectfully requests reconsideration and withdrawal of this rejection.

The Examiner has also rejected claims 1, 3, 5, 26 and 27 under 35 U.S.C. 102(b) as being anticipated by EP0128733/ GenEmbl database accession no. I04090, which discloses an oligonucleotide of 21 bases corresponding to bases 1 – 18 of instant SEQ ID NO:17, with a three base mismatch. As indicated above, Applicant has withdrawn, without prejudice, claims 26 and 27 and has amended claims 1, 3 and 5. The oligonucleotide disclosed in EP0128733/ GenEmbl database accession no. I04090 comprises, at most, 11 consecutive nucleotides complementary to SEQ ID NO:33. Applicant submits that EP0128733/ GenEmbl database accession no. I04090, therefore, does not anticipate the subject matter of amended claims 1, 3 and 5 and respectfully requests reconsideration and withdrawal of this rejection.

The Examiner has further rejected claims 1, 3, 5, 26 and 27 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,391,311, SEQ ID NO:6, which discloses an oligonucleotide of 20 bases corresponding to bases 2-16 of instant SEQ ID NO:28. As indicated above, claims 26 and 27 have been withdrawn, without prejudice, and claims 1, 3 and 5 have been amended. The oligonucleotide disclosed in U.S. Patent No. 6,391,311, SEQ ID NO:6 comprises, at most, 13 consecutive nucleotides complementary to SEQ ID NO:33. Applicant

submits that U.S. Patent No. 6,391,311, SEQ ID NO:6, therefore, does not anticipate the subject matter of amended claims 1, 3 and 5 and respectfully requests reconsideration and withdrawal of this rejection.

CONCLUSION

On the basis of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §121. Applicant respectfully submits that the claims currently on file are ready for examination and in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO Customer Number: 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133